(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 June 2004 (10.06.2004)

PCT

(10) International Publication Number
WO 2004/048369 A1

(51) International Patent Classification[7]: C07D 409/04

(21) International Application Number:
PCT/KR2003/002552

(22) International Filing Date:
25 November 2003 (25.11.2003)

(25) Filing Language: Korean

(26) Publication Language: English

(30) Priority Data:
10-2002-0074119
26 November 2002 (26.11.2002) KR

(71) Applicant *(for all designated States except US)*: **CJ CORPORATION** [KR/KR]; 500, Namdaemunro5-ga, Jung-gu, 100-749 Seoul (KR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KIM, Jin-Wan** [KR/KR]; 406-304 Jugong Apt., Dunchon1-dong, Gangdong-gu, 134-061 Seoul (KR). **CHOI, Kwang-Dong** [KR/KR]; 11-808 Samho Apt., Bisan-dong, Dongan-gu, 431-050 Anyang-city, Kyungki-do (KR). **LIM, Jee-Woong** [KR/KR]; 1025-402 Jugong Apt., Sanbon-dong, 435-040 Gunpo-city, Kyungki-do (KR). **LEE, Kwang-Hyeg** [KR/KR]; 702-402 Mokryunmaeul Hwasung Village, Yatap-dong, Bundang-gu, 463-070 Sungnam-city, Kyungki-do (KR). **LEE, Sang-Ho** [KR/KR]; 301-105 Kwanakseongwon Apt., Buheung-dong, Dongan-gu, 431-054 Anyang-city, Kyungki-do (KR).

(74) Agent: **LEE, Young-Pil**; The Chunghwa Building, 1571-18 Seocho-dong, Seocho-gu, Seoul 137-874 (KR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/048369 A1

(54) Title: METHOD FOR PREPARING OLTIPRAZ

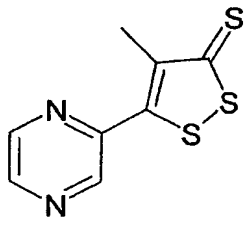
(57) Abstract: Provided is a method for preparing oltipraz. The method includes reacting methyl 2-methyl-3-(pyrazin-2-yl)-3-oxopropionate with phosphorus pentasulfide in the presence of a mixed solvent of toluene and xylene, followed by recrystallization.

METHOD FOR PREPARING OLTIPRAZ

Technical Field

The present invention relates to a method for preparing oltipraz represented by Formula 1 below:

Formula 1



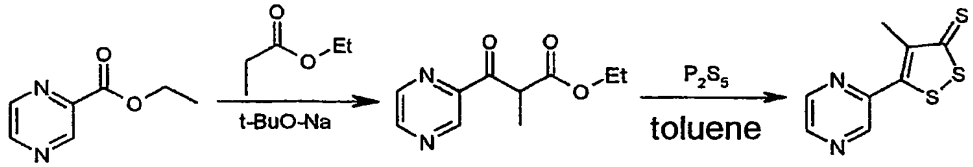
Background Art

Oltipraz represented by Formula 1 above was originally developed as an anti-schistosomal drug that eliminates parasites known blood flukes by Rhone-Poulenc, in 1980. However, during clinical trials, it was found that oltipraz does not have excellent drug effect relative to praziquantel that had been currently used for the treatment of parasite infections, and thus oltipraz was later abandoned.

Thereafter, in studies on a new reaction mechanism of oltipraz conducted in the 1990s, it was reported that oltipraz is effective for the inhibition of HIV propagation [Prochaska et al., 1995], the prevention and treatment of cancers, and the inhibition of HBV transcription [Chi et al., 1998].

Methods for preparing oltipraz are disclosed in U.S. Patent No. 4,110,450, assigned to Rhone-Poulenc, issued in 1978. This patent provides two methods for preparing oltipraz, one of which is as following Scheme 2.

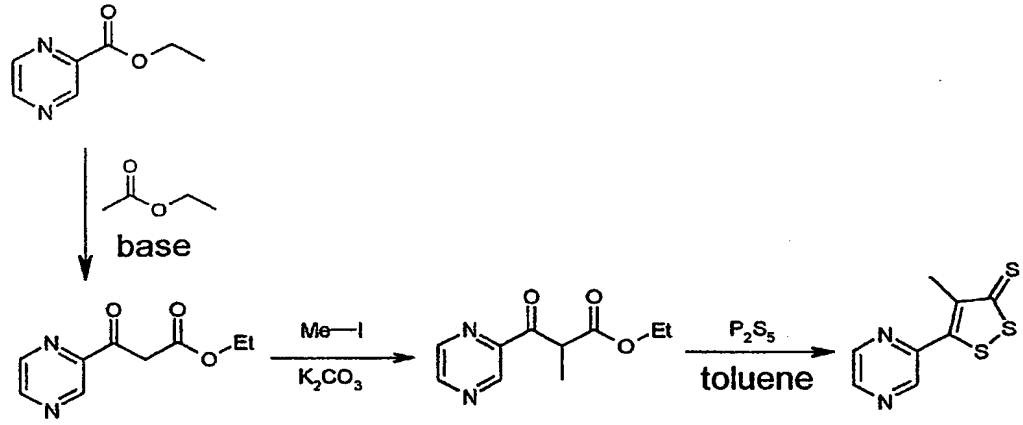
Scheme 2



According to Scheme 2, however, the duration for preparation of oltipraz is too long, as 18 to 24 hours. Also, after a Claisen condensation reaction between ethyl pyrazine-2-carboxylate and ethyl propionate, separation and purification using a column are done. Furthermore, a total yield achieved after two steps of Scheme 2 above is 4.2%, which is too low for mass production.

Another method for preparing oltipraz disclosed in the above patent is as following Scheme 3.

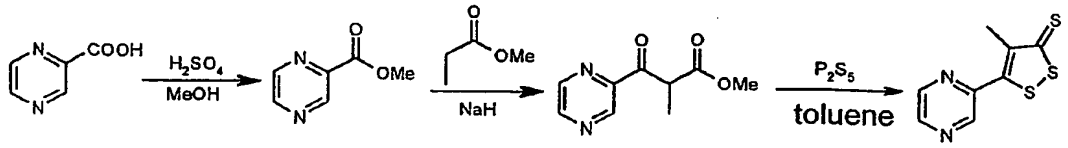
Scheme 3



The method of Scheme 3 includes an additional reaction step, as compared to the method of Scheme 2. Like in Scheme 2, a total yield is too low for mass production.

WO01/09118, issued on August 2001, discloses a method for preparing oltipraz as following Scheme 4:

Scheme 4



In the above method, since sodium hydride is used as a base in a Claisen condensation reaction, there is an explosion risk of hydrogen produced during the condensation reaction. Also, since sodium hydride dispersed in oil is used, a pretreatment for oil removal is required. In particular, excess phosphorus pentasulfide (P_2S_5) inevitably used in the formation of a dithiolethione ring may cause severe environmental contamination. In addition, like in the above-described methods, a lengthy reaction duration is required.

Steps influencing the total yield of oltipraz in oltipraz preparation methods are a Claisen condensation reaction step in the presence of strong base and a dithiolethione ring formation step using P_2S_5.

In formation of dithiolethione rings from 3-oxoester compounds, a method of enhancing the yield of dithiolethione using various reagents such as P_2S_5, Lawesson's reagent, sulfur (S)/ P_2S_5, or hexamethyldisiloxane/ P_2S_5 has been reported [Tetrahedron Letters 2000, p.9965, 17-18]. However, the yield of 3-oxoester compounds with a nitrogen-containing hetero ring is very low, and in particular, the yield of oltipraz with a pyrazinyl group is extremely low, as less than 10%.

Disclosure of the Invention

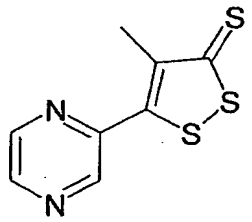
Therefore, while searching for solutions to the above problems, the present inventors developed a novel method for preparing oltipraz in which a 3-oxoester compound can be produced in high yield in the presence of a strong base with no explosion risk, and the duration for formation of a dithiolethiole ring is significantly reduced, and completed the present invention.

The present invention provides a method for preparing oltipraz.

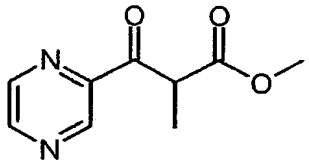
Best mode for carrying out the Invention

The present invention provides a method for preparing oltipraz represented by Formula 1, including reacting methyl 2-methyl -3-(pyrazin-2-yl)-3-oxopropionate represented by Formula 4 with phosphorus pentasulfide (P_2S_5) in the presence of a mixed solvent of toluene and xylene, followed by recrystallization.

Formula 1



Formula 4



Preferably, the volume ratio of toluene to xylene in the mixed solvent is in a range of 1:1 to 1:4.

Since the mixed solvent of toluene and xylene has a high boiling point, a reflux temperature can be efficiently increased. The activity of P_2S_5 increases with increasing reaction temperature. This is supported by the results of experiments using toluene, xylene, tetrahydrofuran, or methylenechloride, that as a reaction temperature increases, the activity of P_2S_5 increases. In this regard, the use of the mixed solvent of toluene and xylene can increase a reaction yield.

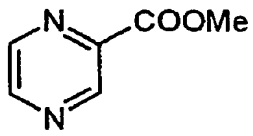
Also, due to the use of the mixed solvent, the reaction duration for formation of dithiolethione is reduced to 4 to 6 hours, which is time effective. This is in contrary to a conventional method requiring 18 to 24 hours for the formation of dithiolethione.

Preferably, P_2S_5 is used in an amount of 0.5 to 3 equivalents, more preferably, 1.05 to 1.50 equivalents, based on 1 equivalent of

methyl 2-methyl -3-(pyrazin-2-yl)-3-oxopropionate.

The methyl 2-methyl-3-(pyrazin-2-yl)-3-oxopropionate of Formula 4 may be produced by a Claisen condensation reaction between methyl pyrazine-2-carboxylate represented by Formula 3 below and methyl propionate in the presence of a strong base.

Formula 3



The strong base may be sodium hydroxide, potassium hydroxide, sodium t-butoxide, potassium t-butoxide, or sodium amide. Potassium t-butoxide is preferred.

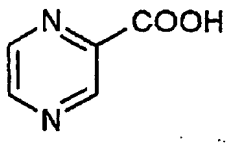
A solvent that can be used in the condensation reaction is a nonreactive solvent commonly used in an organic reaction, i.e., toluene, methylenechloride, or tetrahydrofuran. Tetrahydrofuran is preferred.

A conventional method includes a separation and/or purification step after the Claisen condensation reaction, or another additional reaction step, which creates commercial inefficiency. However, under the above-described optimal reaction condition, a high purity product can be obtained even when a separation and/or purification process is not used. Also, a single solvent can be reused after distilled, thereby contributing to cost curtailment effect.

Preferably, the strong base is used in an amount of 1.5 to 2.5 equivalents, more preferably, 1.8 to 2.0 equivalents, based on 1 equivalent of methyl pyrazine-2-carboxylate.

The methyl pyrazine-2-carboxylate of Formula 3 may be produced by an esterification reaction of pyrazine-2-carboxylic acid represented by Formula 2 below in a methanol solution in the presence of an acid catalyst such a sulfuric acid under reflux.

Formula 2

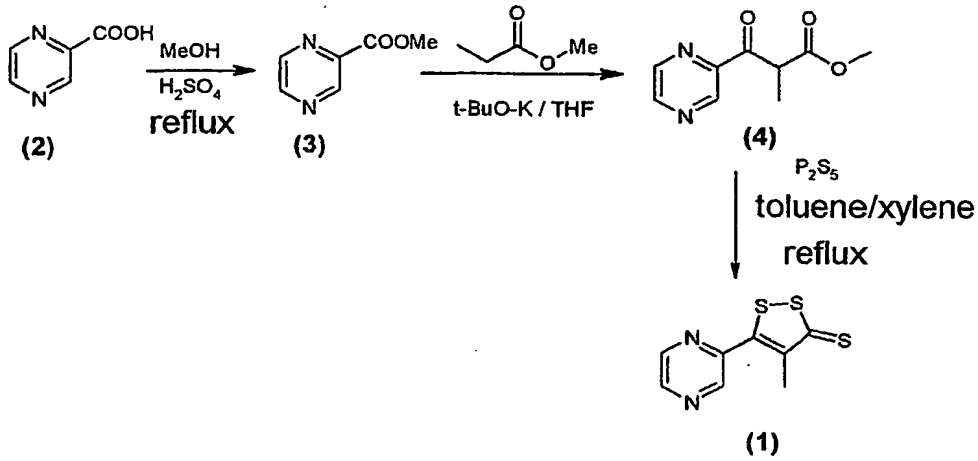


In the esterification reaction, it was found that the amount of an acid catalyst is closely related to a reaction duration. Through studies on increase or decrease of the amount of an impurity, which is a byproduct, with increasing the amount of an acid catalyst, the present inventors found that an increase of the amount of an acid catalyst enables to a reduction of a reaction duration without producing an impurity, which increases a production efficiency relative to the prior art.

The acid catalyst that can be used in the esterification reaction is an inorganic acid commonly commercially available, for example, sulfuric acid, hydrochloric acid, or phosphoric acid. The most preferable acid catalyst is sulfuric acid. Due to an increase of the amount of the acid catalyst, pyrazine-2-carboxylate can be obtained without an increase of an impurity by reflux of 4 to 5 hours, which is in contrary to a conventional reflux time of 48 hours. Preferably, the amount of the acid catalyst is in a range of 5.8×10^{-3} to 25.0×10^{-3} equivalents, based on 1 mole of methyl pyrazine-2-carboxylic acid.

The overall reaction of the above-described method for preparing oltipraz can be summarized as follows.

Scheme 1



After all the reactions are completed, an oltipraz crude crystal is obtained as a final product. A crystallization solvent for the oltipraz crude crystal may be methanol, ethanol, ethylacetate, or acetonitrile. The most preferable crystallization solvent is methanol.

The oltipraz crude crystal may be purified using a recrystallization solvent selected from the group consisting of acetonitrile, methanol, N,N-dimethylformamide, N,N-dimethylacetamide, and a mixed solvent thereof.

When the recrystallization solvent is acetonitrile, it is preferable to use 30 to 40 parts by volume of acetonitrile, based on 1 part by weight of the oltipraz crude crystal.

When the recrystallization solvent is a mixed solvent of N,N-dimethylformamide and acetonitrile, it is preferable to use 15 to 20 parts by volume of N,N-dimethylformamide and 30 and 40 parts by volume of acetonitrile, based on 1 part by weight of the oltipraz crude crystal.

When the recrystallization solvent is a mixed solvent of N,N-dimethylformamide and methanol, it is preferable to use 15 to 20 parts by volume of N,N-dimethylformamide and 30 to 40 parts by volume of methanol, based on 1 part by weight of the oltipraz crude crystal.

If the amount of the recrystallization solvent is outside the above range, the yield of a product significantly reduces. Also, the

recrystallization solvent may be remained in the product.

Hereinafter, the present invention will be described more specifically by examples. However, the following examples are provided only for illustrations and thus the present invention is not limited to or by them.

Example 1

Methyl pyrazine-2-carboxylate (Formula 3)

20.0 g (805.8 mmole) of pyrazine-2-carboxylic acid was added to 160 mL of methanol, and 1.0 mL of a concentrated sulfuric acid was gradually dropwise added thereto with stirring. A reaction solution was refluxed at a temperature of 80 to 85℃ for 5 hours. The reaction solution was cooled to a temperature of 20 to 22℃ and concentrated to a volume of 25mL. Then, 80 mL of methylenechloride and 40 mL of water were added to the resultant concentrate. The resultant solution was then neutralized by gradual addition of 40 mL of a saturated sodium hydrogen carbonate solution to get a pH of 8.5. An organic layer was separated and a water layer was extracted again with 40 mL of methylenechloride. The combined organic layer was dried over anhydrous magnesium sulfate, filtered, and washed with 20 mL of methylenechloride. A filtrate was concentrated to give 21.1 g of the titled compound as a pale brown solid (yield 94.8%).

Melting point: 60 ~ 61℃

Example 2

Methyl 2-methyl-3-(pyrazin-2-yl)-3-oxopropionate (Formula 4)

1.2 L of tetrahydrofuran and 87.8 g (0.78 mole) of potassium t-butoxide were added to a reactor and cooled to 0℃. 71.5 mL (0.74 mol) of methyl propionate was dropwise added to the reactor and stirred at 0℃ for 30 minutes. 60 g (0.434 mole) of the methyl pyrazine-2-carboxylate of Example 1 dissolved in 500 mL of tetrahydrofuran was dropwise added to the reactor for 30 minutes and

stirred at a temperature of 20 to 25℃ for 3 hours. 0.5 L of distilled water and 0.5 L of saturated ammonium chloride solution were added to the reaction solution and stirred for 30 minutes. The resultant reaction solution was concentrated to a volume of 1.0 L and then extracted with 1.0 L of methylenechloride. The resultant extract was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated to give 75.0 g of the titled compound as a dark brown viscous oil (yield 89.0%).

NMR(δ , $CDCl_3$): 1.50(d, 3H), 3.65(s, 3H), 4.70(q, 1H), 8.60(d, 1H), 8.80(d, 1H), 9.21(s, 1H)

Example 3

Synthesis and recrystallization of oltipraz

300 mL of toluene, 350 mL of xylene, and 48.0 g (216 mmole) of phosphorus pentasulfide were added to a reactor and heated to a temperature of 120 to 122℃. 40.0 g (206 mmole) of methyl 2-methyl-3-(pyrazin-2-yl)-3-oxopropionate prepared in Example 2 was dissolved in 100 mL of toluene and then dropwise added to the reactor. The reaction solution was allowed to proceed under reflux at 135℃ for 4 hours and then cooled to 20℃. After addition of 500 mL of distilled water and 500 mL of methanol, the pH of the resultant reaction solution was adjusted to 8.5 with adding a 28% ammonia solution (about 51 mL). An organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. 150 mL of methanol was added to the resultant concentrate, stirred for one hour, and filtered. A filtrate was washed with 100 mL of methanol to give a humid oltipraz crude crystal (12.0 to 13.0 g).

The oltipraz crude crystal was placed in a reactor. 400 mL of acetonitrile was added and dissolved at 80℃. 1.4 g of activated carbon was added and stirred for 30 minutes. The resultant solution was filtered, washed with 100 mL of acetonitrile, crystallized with stirring

at a temperature of 20 to 25℃ for 2 hours, and again stirred at 10℃ for one hour. The obtained crystal was filtered, washed with 20 mL of acetonitrile, and vacuum dried at 40℃ to give 6.37 g of oltipraz (13.6% yield, >99.5% purity).

NMR(δ , $CDCl_3$): 2.51(s, 3H), 8.70(d, 1H), 8.80(d, 1H), 9.21(s, 1H)

Example 4

Recrystallization of oltipraz

An oltipraz crude crystal prepared in the same manner in Example 3 and 180 mL of N,N-dimethylformamide were placed in a reactor and dissolved at 80℃. Then, 1.4 g of activated carbon was added and stirred for 30 minutes. The resultant solution was filtered and washed with 20 mL of N,N-dimethylformamide. 360 mL of acetonitrile was dropwise added at 80℃, crystallized with stirring at 20 to 25℃ for 2 hours, and again stirred at 10℃ for one hour. The resultant crystal was filtered, washed with 20 mL of acetonitrile, and vacuum dried at 40℃ to give 7.15 g of oltipraz (15.6% yield, >99.6% purity).

NMR(δ , $CDCl_3$): 2.51(s, 3H), 8.70(d, 1H), 8.80(d, 1H), 9.21(s, 1H)

Example 5

Recrystallization of oltipraz

An oltipraz crude crystal prepared in the same manner in Example 3 and 180 mL of N,N-dimethylformamide were placed in a reactor and dissolved at 80℃. Then, 1.4 g of activated carbon was added and stirred for 30 minutes. The resultant solution was filtered and washed with 20 mL of N,N-dimethylformamide. 360 mL of methanol was dropwise added at 80℃, crystallized with stirring at 20 to 25℃ for 2 hours, and again stirred at 10℃ for one hour. The resultant crystal was filtered, washed with 20 mL of methanol, and vacuum dried at 40℃ to give 7.53 g of oltipraz (16.1% yield, >99.6% purity).

NMR(δ , $CDCl_3$): 2.51(s, 3H), 8.70(d, 1H), 8.80(d, 1H), 9.21(s, 1H).

Industrial Applicability

According to an oltipraz preparation method of the present invention, there exists no explosion risk of hydrogen produced and a reaction duration is reduced. In addition, impurity separation and purification processes in the interim reaction process are not required, thereby ensuring the economical mass production of oltipraz.

What is claimed is:

1. A method for preparing oltipraz, comprising reacting methyl 2-methyl-3-(pyrazin-2-yl)-3-oxopropionate with phosphorus pentasulfide in the presence of a mixed solvent of toluene and xylene under reflux to produce an oltipraz crude crystal, followed by recrystallization.

2. The method of claim 1, wherein the volume ratio of toluene to xylene in the mixed solvent is in a range of 1:1 to 1:4.

3. The method of claim 1, wherein the methyl 2-methyl-3-(pyrazin-2-yl)-3-oxopropionate is prepared by a condensation reaction of methyl pyrazine-2-carboxylate and methyl propionate in the presence of a strong base.

4. The method of claim 3, wherein the strong base is potassium t-butoxide.

5. The method of claim 3, wherein a solvent for the condensation reaction is tetrahydrofuran.

6. The method of claim 1, wherein a solvent for the recrystallization is selected from the group consisting of acetonitrile, methanol, N,N-dimethylformamide, N,N-dimethylacetamide, and a mixed solvent thereof.

7. The method of claim 6, wherein acetonitrile in an amount of 30 to 40 parts by volume, based on 1 part by weight of the oltipraz crude crystal, is used for the recrystallization.

8. The method of claim 6, wherein a mixed solvent of N,N-dimethylformamide in an amount of 15 to 20 parts by volume and acetonitrile in an amount of 30 to 40 parts by volume, based on 1 part by

weight of the oltipraz crude crystal, is used for the recrystallization.

9. The method of claim 6, wherein a mixed solvent of N,N-dimethylformamide in an amount of 15 to 20 parts by volume and methanol in an amount of 30 to 40 parts by volume, based on 1 part by weight of the oltipraz crude crystal, is used for the recrystallization.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2003/002552

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 409/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7 C07D 409/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean patents and applications for inventions since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN [CASLINK, oltipraz AND (synthesis OR preparation)]
Pubmed [oltipraz AND (synthesis OR preparation)]

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
D, Y	WO 01/09118 A2 (PRENDERGAST) 8 February 2001 See Example 7 on page 86.	1 - 9
D, Y	US 4110450 (RHONE-POULENC INDUSTRIES) 29 August 1978 See Example 1 - 38.	1 - 9
A	CURPHEY et al., 'A new synthesis of 3H-1,2-Dithiole-3-thiones', Tetrahedron Letters, 1993, Vol.34(23), pp.3703-3706 See the whole document.	1 - 9
A	ABDALY et al., 'Synthesis and schistosomicidal activity of 4-methyl-5-(aryl vinyl)-1,2-dithiole-3-thiones', Il Farmaco, 1991, Vol.46(1), pp.63-73 See the whole document.	1 - 9
A	VACCHER et al., 'Preparation and schistosomicidal activity of vinylogues of 1,3-dithio-3-thione', Il Farmaco, 1987, Vol.42(6), pp.397-407 See the whole document.	1 - 9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 FEBRUARY 2004 (10.02.2004)	10 FEBRUARY 2004 (10.02.2004)

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
920 Dunsan-dong, Seo-gu, Daejeon 302-701,
Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
LEE, Mi Jeong
Telephone No. 82-42-481-5601

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2003/002552

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO01/09118A2	08.02.2001	WO01/09118A3	22.11.2001
		AU0064625A5	19.02.2001
US4110450A	29.08.1978	AR224095A1	30.10.1981
		AT348535B	26.02.1979
		AT90277A	15.07.1978
		AU2213877A	17.08.1978
		AU509092B2	17.04.1980
		CA1073906A1	18.03.1980
		CH618699A5	15.08.1980
		CH619463A5	30.09.1980
		DE2705641A1	11.08.1977
		DK55477A	11.08.1977
		EG13739A	31.03.1983
		ES455790A1	16.01.1978
		ES458688A1	16.07.1978
		ES458689A1	16.07.1978
		GB1518071A	19.07.1978
		HK17481A	08.05.1981
		HU172528B	28.09.1978
		IE44561B1	13.01.1982
		IL51403A	16.09.1980
		JP52113982A	24.09.1977
		KE3126A	29.05.1981
		LU76728A1	18.08.1977
		MY182A	31.12.1982
		NL7701107A	12.08.1977
		OA5565A	30.04.1981
		PH12367A	29.01.1979
		PT66175A	01.03.1977
		SE427274B	21.03.1983
		SE7701460A	11.08.1977
		SU683622A3	30.08.1979

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2003/002552

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 409/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7 C07D 409/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean patents and applications for inventions since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN [CASLINK, oltipraz AND (synthesis OR preparation)]
Pubmed [oltipraz AND (synthesis OR preparation)]

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
D, Y	WO 01/09118 A2 (PRENDERGAST) 8 February 2001 See Example 7 on page 86.	1 - 9
D, Y	US 4110450 (RHONE-POULENC INDUSTRIES) 29 August 1978 See Example 1 - 38.	1 - 9
A	CURPHEY et al., 'A new synthesis of 3H-1,2-Dithiole-3-thiones', Tetrahedron Letters, 1993, Vol.34(23), pp.3703-3706 See the whole document.	1 - 9
A	ABDALY et al., 'Synthesis and schistosomicidal activity of 4-methyl-5-(aryl vinyl)-1,2-dithiole-3-thiones', Il Farmaco, 1991, Vol.46(1), pp.63-73 See the whole document.	1 - 9
A	VACCHER et al., 'Preparation and schistosomicidal activity of vinylogues of 1,3-dithio-3-thione', Il Farmaco, 1987, Vol.42(6), pp.397-407 See the whole document.	1 - 9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 FEBRUARY 2004 (10.02.2004)	10 FEBRUARY 2004 (10.02.2004)

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea	LEE, Mi Jeong
Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-5601